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The CXCR4 might be a potential biomarker for esophageal squamous cell carcinoma

A meta-analysis

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Abstract

Objective: To evaluate the relationship between CXCL12/CXCR4 and the progress, prognosis of esophageal squamous cell carcinoma (ESCC), providing evidence for potential early diagnosis, clinical treatment, prognosis evaluation, and therapeutic target of ESCC.

Methods: Databases of PubMed, the Cochrane Library, Embase, and Web of Science were searched for the relationship between CXCL12/CXCR4 and clinicopathological characteristics and survival time of ESCC. Stata16.0 software was used to conduct meta-analysis.

Results: A total of 10 studies involving 1216 cases of patients with ESCC were included in our study. The results indicated that high-level expression of CXCR4 was significantly correlated with tumor differentiation [OR = 0.69, 95% confidence interval (CI): (0.50, 0.97)], tumor infiltration [OR = 0.39, 95% CI: (0.25, 0.61)], lymph node metastasis [OR = 0.36, 95% CI: (0.21, 0.61)], clinical stage [OR = 0.33, 95% CI: (0.24, 0.45)] of ESCC. The expression of CXCR4 was also significantly correlated with OS [HR = 2.00, 95% CI: (1.63, 2.45)] and disease-free survival [HR = 1.76, 95% CI: (1.44, 2.15)] in patients of ESCC after surgical resection. No significant relationship was observed between the expression of CXCL12 and the clinicopathological characteristics of ESCC.

Conclusion: CXCR4 might be a potential biomarker for the progress and prognosis evaluation, and therapeutic target for ESCC.

Abbreviations: 95% CI = 95% confidence interval, CXCL12 = CXC chemokine-12, CXCR4 = CXC chemokine receptor-4, DFS = disease-free survival time, ESCC = esophageal squamous cell carcinoma, HR = hazard ratio, OR = odds ratio, OS = overall survival time, SCC = squamous cell carcinoma, TCGA = The Cancer Genome Atlas.

Keywords: Clinicopathological characteristics, CXCL12, CXCR4, ESCC, meta-analysis, prognosis

1. Introduction

Esophagus carcinoma is a common malignant tumor of the digestive tract with strong invasion and poor prognosis. It is the 7th prevalent cancer and the 6th leading cause of cancer-related death in the world. There are more than 572,000 new cases and 508,000 deaths each year.[1] The 5-year relative survival rate is as low as 20%.[2] There are 2 major types of esophageal cancer existing, squamous cell carcinoma (SCC) and adenocarcinoma. The esophageal squamous cell carcinoma (ESCC) is the most common type, accounting for more than 90% of esophageal carcinoma.[3] The 5-year survival rate of ESCC is about 18%, which is tightly correlated with late diagnosis, aggressiveness, and a lack of effective treatment strategies.[4] Due to the occult onset of ESCC, there are usually no clinical symptoms in the early stage. Once clinical symptoms appear, most patients are in the middle or late clinical stage, and the treatment effect and prognosis are generally limited.[5] Therefore, there is a great need to elucidate the molecular mechanisms and find efficient ESCC tumor biomarkers for the early diagnosis, progress, and prognosis evaluation of ESCC.

CXCL12, also known as stromal cell-derived factor-1 (SDF-1), is a CXC chemokine. CXCL12 and its receptor participate in the occurrence and development of various tumors by promoting proliferation, angiogenesis, invasion, and metastasis.[6]

PC and Y-LZ contributed equally to this work.

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CXCR4 is the major receptor of CXCL12, and it is one of the most widely expressed chemokine receptors in more than 23 human cancers, including breast cancer, ovarian cancer, melanoma, ESCC, and CRC. While it usually expresses low or absent in normal tissues.[7–9] When CXCR4 binds to CXCL12, the CXCL12/CXCR4 axis is activated. The downstream signal pathways are activated, such as PI3k-Akt, Ras/Raf, NF-kB, MAPK, and so on, which influence the tumor occurrence, progress, and prognosis. Thus, CXCL12/CXCR4 axis plays an important role in proliferation, metastasis, prognosis, and recurrence in carcinomas.

Several previous studies have found that CXCL12/CXCR4 axis is highly expressed in ESCC, suggesting important roles in tumor cell proliferation, invasion, metastasis, and prognosis after tumor resection. CXCL12/CXCR4 might be a potential biomarker for the occurrence, progress, prognosis evaluation, and therapy of ESCC. However, due to the limitations of sample size, race of patients, and detection methods, the results of similar studies were inconsistent. Therefore, our study used the method of meta-analysis to systematically evaluate the correlation between the expression of CXCL12/CXCR4 and ESCC to provide evidence for potential early diagnosis, clinical treatment, prognosis evaluation, and therapeutic target of ESCC.

2. Materials and methods

Our meta-analysis was based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[10]

2.1. Studies retrieval strategy

PubMed, the Cochrane Library, EMBASE, and Web of Science were searched by 2 independent researchers (up to March 2022) on the relationship between CXCL12/CXCR4 and clinicopathological characteristics and survival time of ESCC. The following strategy and keywords were used: CXCL12 (Chemokine or SDF-1) OR CXCR4 (CXC chemokine receptor-4 or LESTR) AND Esophageal cancer (Esophageal tumor or Esophageal carcinoma or ESCC or ESCC). No limitation on country, race, and language was added when studies were searched.

2.2. Inclusion and exclusion criteria

The included studies must meet the following criteria: the studies explored the relationship between the expression of CXCL12/CXCR4 and clinicopathological characteristics, the survival time of patients in ESCC; the patients of ESCC were confirmed by pathological diagnosis and the clear criteria for the high or low expression of CXCL12/CXCR4 were provided; the data of clinicopathological characteristics, such as tumor location, tumor size, differentiation, infiltration, clinical stage, lymph node metastasis, HR, and 95% CI of survival time or Kaplan–Meier curve should be reported. The exclusion criteria involved: animal or cell research studies; secondary research, such as meta-analysis, bioinformatics analysis, review, or meeting paper; the expression of CXCL12/CXCR4 was not detected by immunohistochemistry, or the results were not expressed in the form of negative or positive.

2.3. Studies screening and data extraction

A standardized data extraction form was used for data extraction, and 2 researchers completed data extraction, screening, and quality evaluation independently. The extracted data included the name of the first author, year of publication, number of cases, detection methods for the expression of CXCL12 and CXCR4, clinicopathological characteristics, the overall survival time (OS), and disease-free survival time (DFS) of ESCC.

2.4. Variables for statistical analysis

The clinicopathological characteristics of ESCC included tumor size, tumor location, differentiation, infiltration, lymph node metastasis, clinical stages, distant metastasis, vascular invasion, and lymphatic infiltration. The tumor size of ESCC was grouped ≤5 cm and >5 cm. The tumor differentiation was grouped high, medium, and low in the included studies, and high and medium were combined into one group when the pooled effect was calculated. Tumor infiltration was grouped T1, T2, T3, and T4 in the included studies, and T1 and T2 were combined into 1 group and T3 and T4 into another group when the pooled effect was calculated. The clinical stage was grouped stages I, II, II, and IV in the included studies, and I and II were combined into 1 group and II and IV into another group when the pooled effect was calculated. The tumor lymph node metastasis was grouped as negative and positive. The HR of overall survival time was collected or calculated through the Kaplan–Meier curve of survival time.

2.5. Quality assessment

Newcastle Ottawa scale was used to evaluate the risk of bias and included studies by 2 researchers independently.

2.6. Statistical analysis

Stata16.0 software was used to conduct meta-analysis. The relationship between the expression of CXCL12/CXCR4 and the clinicopathological characteristics was expressed by odds ratio (OR) and corresponding 95% confidence interval (CI). The relationship between the expression of CXCR4 and OS, DFS of ESCC was expressed by hazard ratio (HR) and corresponding 95% CI. The statistical significance of OR or HR was analyzed by Z test and P value. I^2 test was used to test the heterogeneity, when $P \leq .05$, it meant significant heterogeneity was observed among included studies, and random effect model was used to combine effect variables; When P value > .05, it meant no significant heterogeneity was observed among included studies, and fixed effect model was used to combine effect variables. Publication bias was evaluated by the Egger test and Begg funnel. The reliability and stability of meta-analysis were evaluated by sensitivity analysis. When P value ≤ .05, it was considered to indicate a statistical difference.

3. Results

3.1. Characteristics of included studies

As shown in Table 1, 9 out of 10 included studies reported the relationship between the expression of CXCR4 and the clinicopathological characteristics of ESCC, only 3 studies about CXCL12. All the 10 studies demonstrated the relationship between the expression of CXCR4 and the survival time of ESCC, but only 2 of them talked about CXCL12. The survival time of ESCC included overall survival (OS) and disease-free survival (DFS). The characteristics and quality evaluation of the studies are also shown in Table 1. The flow diagram is shown in Fig. 1.

3.2. The expression of CXCR4 in ESCC

Because none of the included studies reported the expression of CXCR4 both in ESCC and normal control, meta-analysis could not be conducted. The CXCR4 expressed higher in ESCC than that in normal tissue according to the results in The Cancer Genome Atlas database (http://gepia2.cancer-pku.cn) (Fig. 2).

Table 1

The characteristics and quality evaluation of the included studies.

Studies	Country	Case	Expression of CXCL12	Expression of CXCR4	NOS (scores)
Lu et al[22]	China	154	–	①②③④⑤⑥⑦⑪⑫	7
Yang et al[19]	China	101	–	①②④⑤⑥⑦⑪	7
Uchi et al[42]	Japan	79	①②④⑤⑥⑧⑨⑪	①②④⑤⑥⑧⑨⑪	6
Goto et al[43]	Japan	172	①②⑤⑥⑦⑧⑨⑩	①②⑤⑥⑦⑧⑨⑩⑫	8
Sasaki et al[44]	Japan	214	②④⑤⑥⑦⑨⑩⑫	②④⑤⑥⑦⑨⑩⑫	6
Kaifi et al [45]	Germany	136	–	②④⑤⑥⑩⑪⑫	6
Lu et al[21]	China	127	–	①②③④⑤⑥⑦⑪⑫	7
Zhang et al[23]	China	136	–	①②④⑤⑥⑦⑪⑫	7
Qi et al[24]	China	60	–	①②③⑤⑥⑪	7
Koishi et al[25]	Japan	37	–	⑪	6

① Age; ② gender; ③ tumor size; ④ tumor differentiation; ⑤ tumor infiltration; ⑥ lymph node metastasis; ⑦ tumor clinical stages; ⑧ distant metastasis; ⑨ vascular invasion; ⑩ lymphatic infiltration; ⑪ OS; ⑫ DFS; –:no reported.

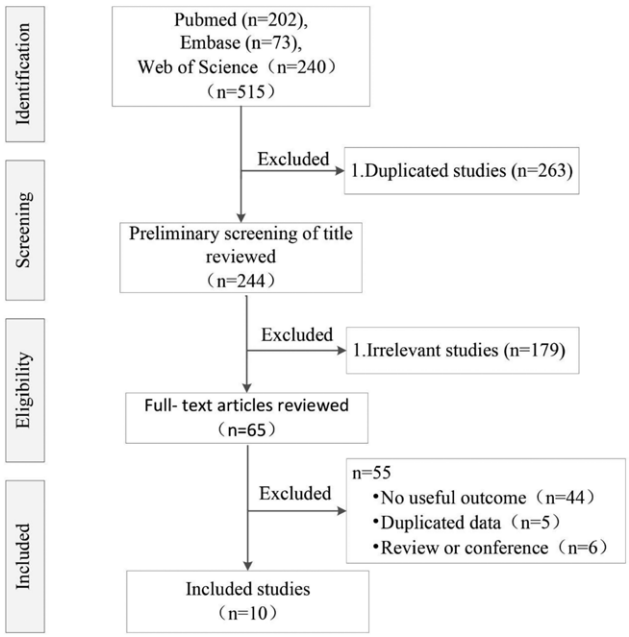

Figure 1. Study design and flow diagram of this study.

3.3. The expression of CXCL12 and clinicopathological characteristics of ESCC

Only 3 studies reported the relationship between the expression of CXCL12 and clinicopathological characteristics. No significant correlation was found between the expression of CXCL12 and gender, differentiation, infiltration, lymph node metastasis, clinical stage, distant metastasis, vascular invasion, and lymphatic infiltration in ESCC patients, $P > .05$ (Table 2).

3.4. The expression of CXCR4 and clinicopathological characteristics of ESCC

Nine out of 10 included studies reported the expression of CXCR4 in male and female ESCC patients, the results indicated that CXCR4 was significantly higher in male than that in female, OR = 1.58, 95% CI: (1.15, 2.15), $P < .01$; 7 studies indicated that CXCR4 was significantly lower in ESCC with high differentiation than those with low differentiation, OR = 0.69, 95% CI: (0.50, 0.97), $P < .01$; 9 studies showed that CXCR4 was significantly lower in ESCC with low infiltration (T1 + T2) than those with high infiltration (T3 + T4), OR = 0.39, 95% CI: (0.25, 0.61), $P < .01$; 9 studies indicated that CXCR4 was significantly lower in ESCC without lymph node metastasis than with lymph node metastasis, OR = 0.36, 95% CI: (0.21, 0.61), $P < .01$; 6 studies indicated that CXCR4 was significantly lower in ESCC with clinical stage (I + II) than that with clinical stage (III + IV), OR = 0.33, 95% CI: (0.24, 0.45), $P < .01$. No significant relationship was observed between the expression of CXCR4 and age, tumor size, distant metastasis, vascular invasion, and lymphatic invasion in ESCC, $P > .05$ (Table 3).

3.5. The expression of CXCR4 and prognosis of ESCC

The results from 8 studies showed that the patients with lower CXCR4 expression of ESCC had a higher overall survival time than that with higher CXCR4 expression, HR = 2.01, 95% CI: (1.61, 2.50), $P < .01$ (Fig. 3); 6 of them indicated that patients with lower CXCR4 expression of ESCC had a higher disease-free survival time than that with higher CXCR4 expression, HR = 1.74, 95% CI: (1.40, 2.15), $P < .01$. (Fig. 4). The OS and DFS of ESCC patients with high expression of CXCR4 were significantly shortened, and the high expression of CXCR4 might be an important marker of poorer prognosis of ESCC (Table 4).

3.6. Publication bias analysis and sensitivity analysis

The results of the Egger test and Begg funnel showed that there was no publication bias was observed in the analysis between the expression of CXCL12 and clinicopathological characteristics of ESCC ($P > .05$). Slight publication bias was found in the analysis of the expression CXCR4 and lymph node metastasis in ESCC, and no significant publication bias was found in the analysis of CXCR4 and other variable ($P > .05$).

By eliminating the influence of individual studies on the results of meta-analysis one by one for sensitivity analysis, the results showed no significant changes, suggesting that the results of this study were stable.

4. Discussion

GTP chemokine is a member of the transmembrane chemokine receptor family, which can selectively promote the expression of GTP chemokine and its target protein. CXCL12 is a common CXC chemokine, which is mainly expressed in fibroblasts, endothelial cells, and tumor cells,[11] participating in angiogenesis and inflammatory response and playing an important role in tumor invasion and metastasis.[12,13] CXCR4, also known as "fusin" is one of the most well-studied chemokine receptors due to its role as a co-receptor for HIV-1 entry.[14] CXCR4 is the main receptor of CXCL12.[15] As a G-protein-coupled receptor (GPCR) the mechanism of CXCR4 receptor activation was mediated by coupling to an intracellular heterotrimeric G-protein associated with

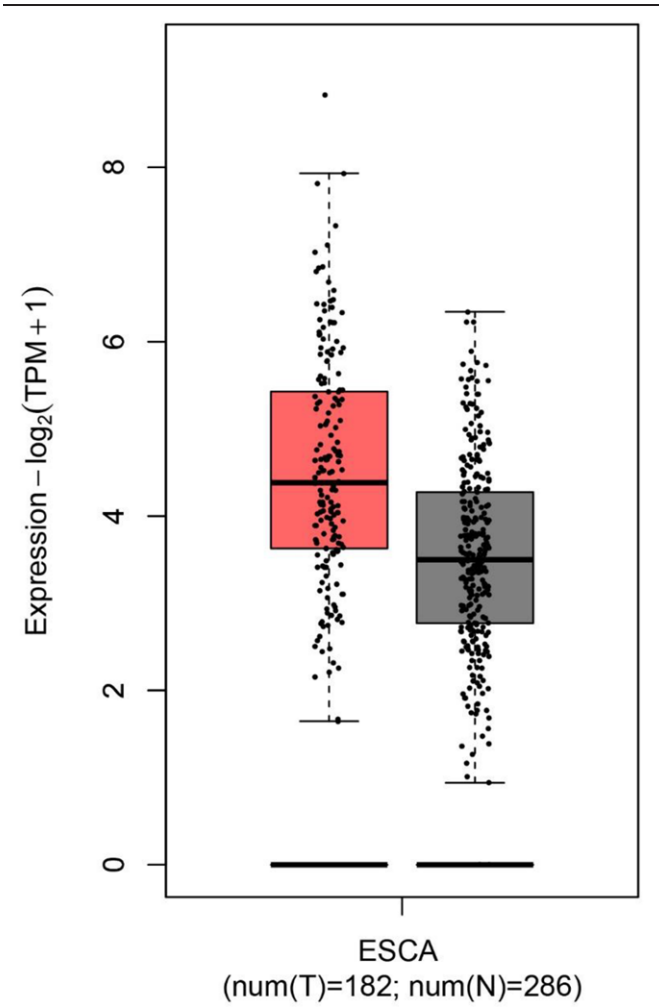

Figure 2. Expression analysis of CXCR4 in ESCC. The expression of CXCR4 in ESCC based on the TCGA (cancer samples) and GTEx (normal tissues) databases.

the inner surface of the plasma membrane. After CXCL12 binding to CXCR4, various downstream signaling pathways were initiated, such as PI3K-Akt, MEK/ERK, Ras, c-Jun N-terminal kinase (JNK), mitogen-activated protein (MAPK), and so on, which regulates the invasion, angiogenesis and metastasis of cancer cells.[16,17] Additionally, CXCL12–CXCR4 axis also regulates apoptosis via Bcl-2 family members.[18] Some studies indicated that CXCR4 was highly expressed in ESCC,[19,20] and the expression level of CXCR4 was related to cell differentiation,[19,21] tumor invasion,[22–24] and poor prognosis[19,22,24,25] of ESCC. The important feature of cancer cells is the significant improvement of proliferation and migration ability. Therefore, CXCL12/CXCR4 may be closely related to the occurrence, development, and prognosis and therapy of ESCC, and it has potential clinical application value in the early diagnosis, progress, and prognosis evaluation of ESCC.

High-level expression of CXCR4 was observed in several cancers and involved in tumor growth and metastasis, especially affecting the survival time of cancer patients. Overexpression of CXCR4 occurs in most breast cancer patients. A study by Xu et al[26] indicated that the OS and DFS in breast cancer patients were negatively correlated to the expression of CXCR4, with the HR 1.65 and 1.94, respectively. Increased CXCR4 expression in PCas was associated with an aggressive phenotype and poor patient survival rates.[27] High levels of CXCR4 were observed in advanced or metastatic ovarian cancers and CXCR4/CXCL12 interactions were shown to regulate metastasis of epithelial ovarian cancer.[28] Such similar results were also observed in lung cancer, gastrointestinal cancers, renal cell carcinoma, and so on, which indicated that CXCR4 might be identified as a poor progress and prognostic biomarker of tumor.

The CXCL12/CXCR4 is also a potential target for cancer therapeutics, and blocking of the CXCL12/CXCR4 axis has shown encouraging results with respect to immunotherapy of glioblastoma,[29,30] ovarian cancer,[31,32] cervical cancer,[33,34] as well as relapsed or refractory multiple myeloma.[35,36] A number of small molecular inhibitors of CXCR4 have been reported to attenuate the growth of tumors in vivo and in vitro, such as WZ811,[37] Butein,[38] MSX-122,[39] Benzenesulfonamides,[40] and so on. The CXCL12/CXCR4 axis is believed to be a novel drug target for cancer therapy. However, very few studies reported the blockade of CXCL12/CXCR4 axis to synergize with chemotherapy or immunotherapy for gastrointestinal cancers, especially for ESCC. We speculated that ESCC might be suppressed by combination therapy involving drugs targeting immunosuppressive CXCL12/CXCR4 axis. Future studies should be taken to target CXCL12–CXCR4 axis in combination with chemotherapy or immunotherapy to treat ESCC.

The results of our meta-analysis indicated that the expression level of CXCR4 was significantly correlated with cell differentiation, tumor infiltration, lymph node metastasis, and clinical stage of ESCC. The high-level expression of CXCR4 was positively correlated with low differentiation, deep invasion, high clinical stage, and lymph node metastasis positive of ESCC, indicating that the high level of CXCR4 was closely related to the development of ESCC. To explore the status of CXCR4 in the prognosis of ESCC, we analyzed the expression of CXCR4, OS, and DFS of ESCC and results demonstrated that the patients of ESCC with high-level expression of CXCR4 had a lower survival rate both in OS and DFS than the patients with the low level or no expression of CXCR4, indicating that high level of CXCR4 showed a poorer prognosis of ESCC. However, no significant correlation was observed between the expression

Table 2

The expression of CXCL12 and clinicopathological characteristics of ESCC.

				Heterogeneity test		Meta-analysis	
Outcome	**Included studies**	***n***	**Effect model**	I^2	***P***	**OR (95% CI)**	***P***
Gender	3	465	Random	60.0%	.08	1.31 (0.40, 4.31)	.66
Differentiation	2	293	Fixed	0.0%	.99	0.70 (0.35, 1.40)	.31
Infiltration	3	465	Fixed	24.3%	.27	1.09 (0.74, 1.62)	.66
Lymph node metastasis	3	465	Random	79.0%	.01	0.77 (0.31, 1.92)	.57
Clinical stages	2	386	Random	84.3%	.01	0.73 (0.24, 2.19)	.58
Distant metastasis	2	386	Fixed	0.00%	.83	0.61 (0.37, 1.01)	.05
Vascular invasion	3	403	Fixed	0.00%	.88	1.32 (0.86, 2.04)	.21
Lymphatic infiltration	3	403	Random	61.7%	.07	1.21 (0.57, 2.58)	.63

Table 3

The expression of CXCR4 and clinicopathological characteristics of ESCC.

Outcome	Included studies	*n*	Effect model	Heterogeneity test		Meta-analysis	
				I^2	*P*	OR (95% CI)	*P*
Age	6	750	Fixed	0.0%	.58	0.95 (0.69, 1.31)	.76
Gender	9	1179	Fixed	0.0%	.66	1.58 (1.15, 2.15)	<.01*
Tumor size	2	214	Random	73.8%	.05	0.97 (0.27, 3.52)	.96
Differentiation	7	947	Fixed	5.1%	.39	0.69 (0.50, 0.97)	<.01*
Infiltration	9	1194	Random	61.4%	<.01	0.39 (0.25, 0.61)	<.01*
Lymph node metastasis	9	1179	Random	72.0%	<.01	0.36 (0.21, 0.61)	<.01*
Clinical stages	6	904	Fixed	43.7%	.11	0.33 (0.24, 0.45)	<.01*
Distant metastasis	2	386	Random	68.5%	.08	0.89 (0.25, 3.16)	.85
Vascular invasion	3	403	Fixed	0.0%	.61	0.92 (0.56, 1.52)	.74
Lymphatic infiltration	4	539	Random	80.5%	<.01	0.77 (0.30, 1.95)	.58

*$P < .05$, significantly statistical difference was observed.

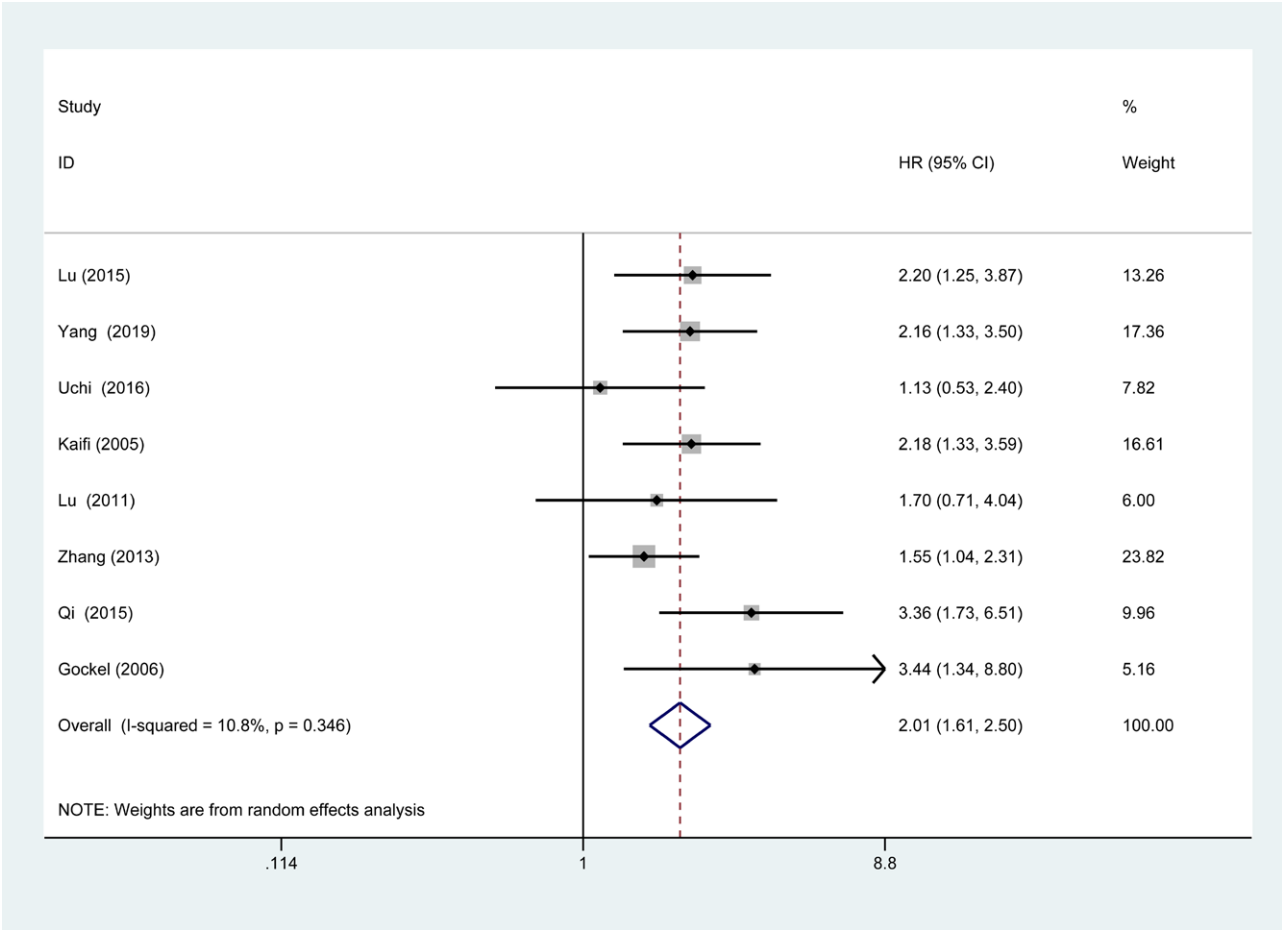

Figure 3. Expression analysis of CXCR4 and OS in ESCC. The patients of ESCC with high expression of CXCR4 showed a shorter overall survival time (OS).

of CXCL12 and the clinicopathological characteristics of ESCC. Wang et al[41] also reported that silencing CXCR4 gene expression by lentivirus shRNA inhibited the proliferation of the EC9706 human esophageal carcinoma cell line and reduced the growth of tumor xenografts in mouse models. CXCR4 may be a potential biomarker in the early diagnosis, progress, and prognosis evaluation, therapy target of ESCC.

Although efforts had been made, there were still some limitations existing in our study: due to the limitation of published studies, only 10 studies were included in our studies explore the relationship between CXCR4 expression and ESCC, and 3 studies for the relationship between CXCL12 and ESCC. The sample size was relatively small, some bias might exist; due to different criteria for judging the positive or negative of CXCR4, the cutoff value of immunohistochemical results used in the included studies was not clearly reported, which may affect the accuracy of the results; due to the difference in cutoff value, follow-time, and race of subjects in included studies, the included studies had some heterogeneity; some of the included studies only reported the Kaplan–Meier curve of survival analysis and did not report detailed survival data of OS and DFS. We inferred the HR and 95% CI of OS and DFS through the Kaplan–Meier curve, which might overestimate or underestimate the real OS and DFS.

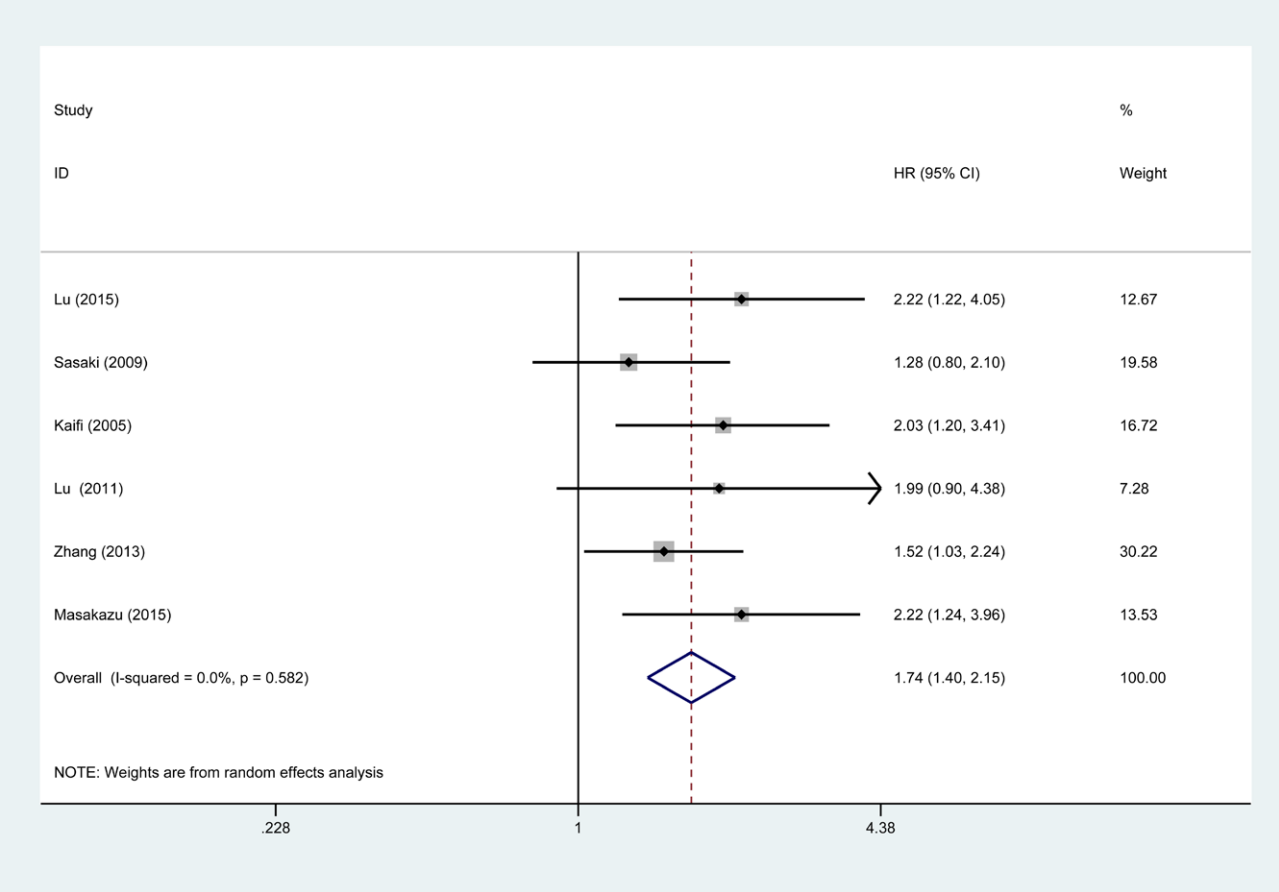

Figure 4. Expression analysis of CXCR4 and DFS in ESCC. The patients of ESCC with high expression of CXCR4 showed a shorter disease-free survival time (DFS).

Table 4

The expression of CXCR4 and prognosis in ESCC.

				Heterogeneity test		Meta-analysis	
Outcome	**Included studies**	***n***	**Effect model**	***I²***	***P***	**HR (95% CI)**	***P***
OS	8	830	Fixed	10.8%	.35	2.01 (1.61, 2.50)	<.01*
DFS	6	1093	Fixed	0.0%	.69	1.74 (1.40, 2.15)	<.01*

*$P < .05$, significantly statistical difference was observed.

5. Conclusion

CXCL12/CXCR4 axis is closely related to the occurrence, development, and prognosis of ESCC. CXCR4 is significantly expressed higher in ESCC than normal tissue, suggesting serious progress and poor prognosis of ESCC. The CXCR4 might be a potential biomarker for the progress and prognosis evaluation and therapeutic target for ESCC. Due to the limitation of the sample size and quality of included studies, our conclusions still need to be verified by high-quality studies.

Author contributions

Data curation: Pei Chen, Ying Guo.
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Funding acquisition: Pei Chen.
Investigation: Ying Guo.
Methodology: Yu-Ling Zhang.
Project administration: Yu-Ling Zhang.
Visualization: Pei-Pei Tang.
Writing—original draft: Pei Chen.
Writing—review & editing: Yu-Ling Zhang.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
[2] Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7–33.
[3] Smyth EC, Lagergren J, Fitzgerald RC, et al. Oesophageal cancer. Nat Rev Dis Primers. 2017;3:17048.
[4] Liu Y, Xiong Z, Beasley A, et al. Personalized and targeted therapy of esophageal squamous cell carcinoma: an update. Ann N Y Acad Sci. 2016;1381:66–73.
[5] Alaouna M, Hull R, Penny C, et al. Esophageal cancer genetics in South Africa. Clin Exp Gastroenterol. 2019;12:157–77.
[6] Meng W, Xue S, Chen Y. The role of CXCL12 in tumor microenvironment. Gene. 2018;641:105–10.

[7] Chen IX, Chauhan VP, Posada J, et al. Blocking CXCR4 alleviates desmoplasia, increases T-lymphocyte infiltration, and improves immunotherapy in metastatic breast cancer. Proc Natl Acad Sci U S A. 2019;116:4558–66.
[8] Yu X, Wang D, Wang X, et al. CXCL12/CXCR4 promotes inflammation-driven colorectal cancer progression through activation of RhoA signaling by sponging miR-133a-3p. J Exp Clin Cancer Res. 2019;38:32.
[9] Sad LMAE, Mohamed DA, Elanwar NM, et al. CXCR4 and RIF1 overexpression induces resistance of epithelial ovarian cancer to cisplatin-based chemotherapy. J Cancer Res Ther. 2021;17:1454–61.
[10] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
[11] Mehrpouri M. The contributory roles of the CXCL12/CXCR4/CXCR7 axis in normal and malignant hematopoiesis: a possible therapeutic target in hematologic malignancies. Eur J Pharmacol. 2022;920:174831.
[12] Muller A, Homey B, Soto H, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature. 2001;410:50–6.
[13] Luker KE, Luker GD. Functions of CXCL12 and CXCR4 in breast cancer. Cancer Lett. 2006;238:30–41.
[14] Chen B. Molecular mechanism of HIV-1 entry. Trends Microbiol. 2019;27:878–91.
[15] Fang HY, Munch NS, Schottelius M, et al. CXCR4 is a potential target for diagnostic PET/CT imaging in Barrett's dysplasia and esophageal adenocarcinoma. Clin Cancer Res. 2018;24:1048–61.
[16] Liu ZY, Yang QX, Cao Y, et al. CXCR4 protects bone marrow-derived endothelial progenitor cells against hypoxia through the PI3K/Akt signaling pathway. Exp Ther Med. 2021;2:1200.
[17] Bianchi ME, Mezzapelle R. The chemokine receptor CXCR4 in cell proliferation and tissue regeneration. Front Immunol. 2020;11:2109.
[18] Kremer KN, Peterson KL, Schneider PA, et al. CXCR4 chemokine receptor signaling induces apoptosis in acute myeloid leukemia cells via regulation of the Bcl-2 family members Bcl-XL, Noxa, and Bak. J Biol Chem. 2013;288:22899–914.
[19] Yang X, Lu Q, Xu Y, et al. Clinicopathologic significance of CXCR4 expressions in patients with esophageal squamous cell carcinoma. Pathol Res Pract. 2020;216:152787.
[20] Wu X, Zhang H, Sui Z, et al. CXCR4 promotes the growth and metastasis of esophageal squamous cell carcinoma as a critical downstream mediator of HIF-1α. Cancer Sci. 2022;113:926–39.
[21] Lu CL, Ji Y, Ge D, et al. The expression of CXCR4 and its relationship with matrix metalloproteinase-9/vascular endothelial growth factor in esophageal squamous cell cancer. Dis Esophagus. 2011;24:283–90.
[22] Lu C, Xu F, Gu J, et al. Clinical and biological significance of stem-like CD133(+)CXCR4(+) cells in esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg. 2015;150:386–95.
[23] Zhang L, Ye SB, Ma G, et al. The expressions of MIF and CXCR4 protein in tumor microenvironment are adverse prognostic factors in patients with esophageal squamous cell carcinoma. J Transl Med. 2013;11:60.
[24] Qi J, Li H, Liu N, et al. The implications and mechanisms of the extra-nuclear nucleolin in the esophageal squamous cell carcinomas. Med Oncol. 2015;32:45.
[25] Koishi K, Yoshikawa R, Tsujimura T, et al. Persistent CXCR4 expression after preoperative chemoradiotherapy predicts early recurrence and poor prognosis in esophageal cancer. World J Gastroenterol. 2006;12:7585–90.
[26] Xu TP, Shen H, Liu LX, et al. The impact of chemokine receptor CXCR4 on breast cancer prognosis: a meta-analysis. Cancer Epidemiol. 2013;37:725–31.
[27] Akashi T, Koizumi K, Tsuneyama K, et al. Chemokine receptor CXCR4 expression and prognosis in patients with metastatic prostate cancer. Cancer Sci. 2008;99:539–42.
[28] Barbolina MV, Kim M, Liu Y, et al. Microenvironmental regulation of chemokine (C-X-C-motif) receptor 4 in ovarian carcinoma. Mol Cancer Res. 2010;8:653–64.
[29] Jacobs SM, Wesseling P, de Keizer B, et al. CXCR4 expression in glioblastoma tissue and the potential for PET imaging and treatment with [68 Ga] Ga-Pentixafor/[177 Lu] Lu-Pentixather. Eur J Nucl Med Mol Imaging. 2022;49:481–91.
[30] Daniele S, La Pietra V, Piccarducci R, et al. CXCR4 antagonism sensitizes cancer cells to novel indole-based MDM2/4 inhibitors in glioblastoma multiforme. Eur J Pharmacol. 2021;897:173936.
[31] Zeng Y, Li B, Liang Y, et al. Dual blockade of CXCL12-CXCR4 and PD-1-PD-L1 pathways prolongs survival of ovarian tumor-bearing mice by prevention of immunosuppression in the tumor microenvironment. FASEB J. 2019;33:6596–608.
[32] Reeves PM, Abbaslou MA, Kools FRW, et al. CXCR4 blockade with AMD3100 enhances taxol chemotherapy to limit ovarian cancer cell growth. Anticancer Drugs. 2017;28:935–42.
[33] Lecavalier-Barsoum M, Chaudary N, Han K, et al. Targeting the CXCL12/CXCR4 pathway and myeloid cells to improve radiation treatment of locally advanced cervical cancer. Int J Cancer. 2018;143:1017–28.
[34] Lecavalier-Barsoum M, Chaudary N, Han K, et al. Targeting CXCL12/CXCR4 and myeloid cells to improve the therapeutic ratio in patient-derived cervical cancer models treated with radio-chemotherapy. Br J Cancer. 2019;121:249–56.
[35] Ito S, Sato T, Maeta T. Role and therapeutic targeting of SDF-1α/CXCR4 axis in multiple myeloma. Cancers (Basel). 2021;13:1793.
[36] Beider K, Rosenberg E, Bitner H, et al. The sphingosine-1-phosphate modulator FTY720 targets multiple myeloma via the CXCR4/CXCL12 pathway. Clin Cancer Res. 2017;23:1733–47.
[37] Li SH, Dong WC, Fan L, et al. Suppression of chronic lymphocytic leukemia progression by CXCR4 inhibitor WZ811. Am J Transl Res. 2016;8:3812–21.
[38] Chua AW, Hay HS, Rajendran P, et al. Butein downregulates chemokine receptor CXCR4 expression and function through suppression of NF-kappaB activation in breast and pancreatic tumor cells. Biochem Pharmacol. 2010;80:1553–62.
[39] Liang Z, Zhan W, Zhu A, et al. Development of a unique small molecule modulator of CXCR4. PLoS One. 2012;7:e34038.
[40] Mooring SR, Liu J, Liang Z, et al. Benzenesulfonamides: a unique class of chemokine receptor type 4 inhibitors. ChemMedChem. 2013;8:622–32.
[41] Wang DF, Lou N, Qiu MZ, et al. Effects of CXCR4 gene silencing by lentivirus shRNA on proliferation of the EC9706 human esophageal carcinoma cell line. Tumour Biol. 2013;34:2951–9.
[42] Uchi Y, Takeuchi H, Matsuda S, et al. CXCL12 expression promotes esophageal squamous cell carcinoma proliferation and worsens the prognosis. BMC Cancer. 2016;16:514.
[43] Goto M, Yoshida T, Yamamoto Y, et al. CXCR4 expression is associated with poor prognosis in patients with esophageal squamous cell carcinoma. Ann Surg Oncol. 2017;24:832–40.
[44] Sasaki K, Natsugoe S, Ishigami S, et al. Expression of CXCL12 and its receptor CXCR4 correlates with lymph node metastasis in submucosal esophageal cancer. J Surg Oncol. 2008;97:433–8.
[45] Kaifi JT, Yekebas EF, Schurr P, et al. Tumor-cell homing to lymph nodes and bone marrow and CXCR4 expression in esophageal cancer. J Natl Cancer Inst. 2005;97:1840–7.